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Original Investigations

Thiazide Therapy Is Not a Cause of Arrhythmia in Patients With Systemic Hypertension

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• **Forty-four patients with uncomplicated systemic hypertension underwent 48-hour electrocardiographic monitoring before and after four weeks of treatment with hydrochlorothiazide, 100 mg daily. Plasma potassium concentration decreased from 4.07±0.26 mmol/L (4.07±0.26 mEq/L) to 3.36±0.44 mmol/L (3.36±0.44 mEq/L). The average number of premature ventricular contractions, couplets, or ventricular tachycardia episodes did not change significantly. Twenty patients had more than minimal ventricular ectopy (class 2 to 5) before and 17 after diuretic therapy. Further analysis revealed that following diuretic therapy, neither patients with plasma potassium levels of 3.4 mmol/L or less (≤3.4 mEq/L) nor patients with left ventricular hypertrophy had increased ectopy as compared with baseline. At baseline, patients with left ventricular hypertrophy had more arrhythmias than patients without. We conclude that the results of this study provide no evidence that diuretic therapy or diuretic-induced hypokalemia results in increased ventricular ectopy, and that patients with left ventricular hypertrophy may have more ventricular ectopy than patients without, but these arrhythmias are not adversely effected by diuretic therapy.**

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Diuretics have been widely used in the management of systemic hypertension for more than 20 years. In general, they have been considered to be safe and effective with rather a low side effect profile. They have been used in most studies that showed beneficial effects from the treatment of hypertension,[1,2] and diuretics have been routinely recommended as initial therapy in the stepped-care approach.[3] In recent years, however, the safety of diuretics in the management of hypertension has been questioned. While biochemical consequences such as hyperuricemia, hyperglycemia, or increase in cholesterol levels cause some concern, hypokalemia became a major issue. Fears that mild-to-moderate hypokalemia may aggravate cardiac arrhythmias have resulted in the extensive administration of potassium supplements and potassium-sparing diuretics,[4] and more recently, these fears have initiated a trend away from the use of diuretics in the treatment of hypertension. This trend gained popularity even though an association between hypokalemia and cardiac arrhythmias not only remains unproved but also has been challenged.[4-6] Although some studies suggested an increased risk of cardiac arrhythmias in patients with diuretic-induced hypokalemia,[7,8] others failed to confirm it[9,10] and the subject remains controversial. The original publication of the Multiple Risk Factor Intervention Trial[11] has been interpreted as indicating an increased risk of sudden death in hypertensive patients with resting electrocardiographic (ECG) abnormalities when treated aggressively with diuretics. Although this interpretation has been criticized,[5] this study greatly influenced the medical community.

The present study was designed to investigate the effect of diuretic therapy and diuretic-induced hypokalemia on cardiac arrhythmias by direct recording methods in patients with uncomplicated essential hypertension. Some data from the first 31 patients have been previously published.[12] This article presents complete analysis of the expanded series of 44 patients; particular emphasis has been placed on the influence of diuretic-induced hypokalemia on cardiac arrhythmias.

For editorial comment see p 1265.

PATIENTS AND METHODS

Forty-seven patients with essential hypertension entered the study. All patients were black males. Patients with a history of myocardial infarction, angina pectoris, congestive heart failure, renal insufficiency (creatinine level ≥176.8 μmol/L [≥2.0 mg/dL]), inability to give informed consent, or patients who required digitalis therapy were excluded from the study. Three patients were terminated from the trial because of noncompliance and failure to attend clinic visits.

Screening Phase

Following the history and physical examination, a chest roentgenogram, M-mode echocardiogram, ECG, complete blood cell count, and blood chemistry studies were obtained from all patients. Patients with evidence of heart disease other than left ventricular hypertrophy were excluded from the study. The presence or

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absence of left ventricular hypertrophy was determined from the echocardiogram by measuring the left ventricular posterior wall thickness prior to the mechanical contraction of the left atrium.[13] Left ventricular hypertrophy was considered present if the posterior wall thickness was equal or more than 12 mm. Echocardiograms with evidence of asymmetric hypertrophy or dilated cardiomyopathy were not acceptable. The presence or absence of left ventricular hypertrophy was also determined by ECG criteria using Estes' scoring system.[14]

Study Protocol

Phase 1: Baseline.—After eligibility for the study was determined, all drug therapy was discontinued and potassium chloride, 40 mEq, was given to all patients for ten days. Three weeks later patients were seen for baseline studies. Sitting blood pressure, heart rate, body weight, and plasma creatinine, sodium, potassium, and chloride levels were determined. Blood samples, which were collected in sterilized 10-mL tubes that contained 143 U of lithium heparin, were analyzed within 30 minutes. Shortly after blood samples were obtained, a 48-hour ambulatory ECG monitoring was initiated. Immediately after the completion of the 48-hour recording, a second blood sample for electrolyte determination was obtained. The average plasma potassium level of these two measurements constituted the plasma potassium value of this phase.

Phase 2: Hydrochlorothiazide Therapy.—Following the completion of phase 1, all patients were started on a regimen of hydrochlorothiazide, 50 mg twice daily, that continued for four weeks. At the end of this period and while hydrochlorothiazide therapy continued, all studies described in phase 1, including 48-hour ECG monitoring, were repeated.

Ambulatory ECG Monitoring.—Ambulatory ECG monitoring was carried out for 48 hours during each phase using a double-channel recorder (model 445B; Del Mar Avionics, Irvine, Calif) and analysis was performed on a two-channel cardioscanner (model MK3 Cardiodata Corp, Malboro, Mass). Analysis of all tapes was carried out by an experienced technician. For quality control, 10% of the tapes were analyzed by a second technician. Less than 10% interobserver variability was found in premature beats and no difference was found in couplets or ventricular tachycardia episodes. In addition, samples from each hour recording, including the important arrhythmias, were printed on hard copy in real time and were reviewed by one of us. Ventricular arrhythmias were tabulated in two ways. The first way is modification of Lown's classification as used by Singh et al,[15] which is as follows: 0 indicates no arrhythmias; 1, premature ventricular contractions (PVCs) of 1 to 29/h; 2, PVCs of 30 or more/h; 3, multifocal PVCs; 4, couplets; and 5, ventricular tachycardia. From this grading system an average grade per hour was calculated. The second way is the average number of premature ventricular contractions per hour, total number of couplets, and total number of ventricular tachycardia episodes.

Statistical analysis of the results was performed where appropriate using the Student t test for paired observations, or the χ^2 test. The study was approved by the Research and Development Committee at the Veterans Administration Medical Center, Washington, DC.

RESULTS

At baseline, all patients studied had mild-to-moderate hypertension, normal plasma potassium levels, and normal renal function. Twenty-eight of these patients had evidence of left ventricular hypertrophy by echocardiography and 20 by ECG criteria. The remaining 16 patients had normal left ventricular wall thickness by echocardiography and only one met the ECG criteria for left ventricular hypertrophy. In the group as a whole, body weight and blood pressure decreased significantly as expected with diuretic therapy (Table 1). The plasma potassium level also decreased from 4.07 ± 0.26 mmol/L (4.07 ± 0.26 mEq/L) at baseline to 3.36 ± 0.44 mmol/L (3.36 ± 0.44) ($P<.001$) with hydrochlorothiazide. Premature ventricular contractions averaged 11.3 ± 40.2 before and 7.5 ± 18.8 after hydrochlorothiazide (P = not significant). A total of 129 couplets and seven brief episodes (three to five beats) of ventricular tachycardia was noted before and 18 couplets and three runs of ventricular tachycardia were noted after diuretic therapy. The average grade per hour was similar between the two phases.

Table 1.—Ventricular Ectopy Before and After Diuretic Therapy: All Patients (n = 44)

Variable*	Baseline	Diuretic
SBP, mm Hg	154 ± 16	136 ± 12†
DBP, mm Hg	98 ± 8	89 ± 6†
BW, kg	87.6 ± 16.9	85.9 ± 16.9†
PK, mmol/L (mEq/L)	4.07 ± 0.26	3.36 ± 0.44†
PVC/h	11.3 ± 40.2	7.5 ± 18.8
Total couplets	129	18
Total VT episodes	7	3
AGR/h	0.63 ± 0.70	0.58 ± 0.67

*SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BW, body weight; PK, plasma potassium; PVC, premature ventricular contractions; VT, ventricular tachycardia; and AGR, average grade.
†$P<.001$.

Table 2.—Ventricular Ectopy in Patients With or Without Hypokalemia Receiving Diuretic Therapy

	Hypokalemia (n = 27)		No Hypokalemia (n = 17)	
Variable*	Baseline	Diuretic	Baseline	Diuretic
BW, kg	92.2 ± 17.5	90.1 ± 17.6†	81.1 ± 14.4	79.8 ± 14.1†
PK, mmol/L (mEq/L)	4.00 ± 0.22	3.08 ± 0.24†	4.20 ± 0.28	3.81 ± 0.28†
PVC/h	16.8 ± 50.7	9.1 ± 22.9	2.6 ± 5.9	5.1 ± 9.2
Total couplets	124	12	5	6
Total VT episodes	2	2	5	1
AGR/h	0.72 ± 0.78	0.59 ± 0.64	0.48 ± 0.54	0.57 ± 0.76

*BW indicates body weight; PK, plasma potassium; PVC, premature ventricular contractions; VT, ventricular tachycardia; and AGR, average grade.
†$P<.001$; statistics compare values before and after diuretic therapy.

Assessment of the Effect of Hypokalemia on Ventricular Arrhythmias

To further evaluate the role of low potassium levels on ventricular ectopy patients have been grouped into those who developed hypokalemia while receiving diuretic therapy and those who maintained plasma potassium levels within the normal range (Table 2). Of the 44 patients, 27 had potassium levels of 3.4 mmol/L or less (≤3.4 mEq/L) following thiazide therapy. The decrease in body weight and plasma potassium level was highly significant in both groups ($P<.001$). Ventricular ectopy, and the average grade per hour decreased substantially in the hypokalemic group, although the changes did not reach statistical significance. The distribution of patients into the Lown classes did not change with thiazide therapy (Table 3). In the hypokalemic group, 12 patients had more than minimal ectopy (class 2 to 5) before thiazide therapy and 11 patients had more than minimal ectopy after thiazide therapy. Similarly, in the normokalemic group, eight patients had class 2 to 5 ectopy before thiazide therapy and six patients had it after.

Table 3.—Patient Distribution: Modified Lown Classification*

	Hypokalemic Group		Normokalemic Group	
Class	Baseline	Diuretic	Baseline	Diuretic
0	3	4	0	0
1	12	12	9	11
2	1	1	0	0
3	5	3	3	2
4	4	6	1	3
5	2	1	4	1

*Difference within or between groups not statistically significant. Modification of classification as used by Singh et al.[15]

Table 4.—Ventricular Ectopy in Patients With or Without LVH Before and After Hydrochlorothiazide*

	LVH (n=28)		No LVH (n=16)	
Variable	Baseline	Diuretic	Baseline	Diuretic
LVPWT	1.39±0.14	...	1.03±0.07	...
BW, kg	86.3±14.7	85.4±14.7†	90.0±20.8	88.1±20.6†
PK, mmol/L (mEq/L)	4.06±0.23	3.39±0.45†	4.10±0.32	3.33±0.43†
PVC/h	16.6±49.8	10.1±22.9	2.1±5.0	3.0±5.9
Total couplets	123	15	6	3
Total VT episodes	5	3	2	0
AGR/h	0.79±0.78	0.68±0.74	0.34±0.40†	0.41±0.54

*LVH indicates left ventricular hypertrophy; LVPWT, left ventricular posterior wall thickness; BW, body weight; PK, plasma potassium; PVC, premature ventricular contractions; VT, ventricular tachycardia; and AGR, average grade.

†$P<.001$, compare values before and after diuretic; $P<.05$, compare values between groups at baseline.

Effect of Diuretic Therapy in Patients With or Without Left Ventricular Hypertrophy

Since some studies suggested a higher incidence of ventricular arrhythmias in patients with left ventricular hypertrophy, patients were also grouped into those with and those without left ventricular hypertrophy as assessed by echocardiography (Table 4). Twenty-eight patients met the echocardiographic criteria for left ventricular hypertrophy. Of these patients, 20 also had ECG evidence of left ventricular hypertrophy. In the remaining 16 patients, left ventricular wall thickness was normal, but one patient met ECG criteria for left ventricular hypertrophy. Comparing the ventricular ectopy between the two groups, patients with left ventricular hypertrophy determined by echocardiography had more PVCs per hour and more repetitive beats than patients without left ventricular hypertrophy, but the differences did not reach statistical significance. The difference in the average grade per hour, however, which is an alternative way of quantitating the severity of arrhythmias, was statistically significant. The average grade per hour at baseline was 0.79±0.78 for the first group and 0.34±0.40 for the second ($P<.05$). There were no statistically significant differences in arrhythmias between patients with or without left ventricular hypertrophy determined by ECG.

Diuretic therapy resulted in a significant decrease in body weight and the plasma potassium level in both groups. Arrhythmias, however, did not change significantly. Table 5 shows the patient distribution into arrhythmia classes

Table 5.—Patient Distribution: Modified Lown Classification*

	LVH† Group		Non-LVH† Group	
Class	Baseline	Diuretic	Baseline	Diuretic
0	2	2	1	2
1	11	14	10	9
2	1	0	0	1
3	6	3	2	2
4	4	7	1	2
5	4	2	2	0

*Difference between groups or within groups did not reach statistical significance by χ^2 test. Modification of classification as used by Singh et al.[15]

†LVH indicates left ventricular hypertrophy.

Table 6.—Spontaneous Variability Between 24-Hour Holter Recording Obtained During the Same Phase of the Study*

Patient†	PVC/h	Total Couplets	Total VT Episodes
1			
a	55	10	1
b	99	...	...
2			
a	359	63	...
b	155	18	...
3			
a	8	1	...
b	3	...	...
4			
a	33	...	...
b	90	4	...
5			
a	6	...	2
b	2	...	...
6			
a	8	...	1
b	2	...	...

*PVC indicates premature ventricular contractions; VT, ventricular tachycardia.

†a indicates first Holter monitoring; b, second Holter monitoring.

before and after diuretic therapy in the two groups. Overall, in the left ventricular hypertrophy group, there were 15 patients with more than minimal ventricular ectopy (class 2 to 5) at baseline and 12 after diuretic therapy. In the second group, there were five patients with more than minimal ectopic activity at baseline and five after diuretic therapy. These differences were not statistically significant either within groups or between groups.

Data of this study demonstrated no correlation between plasma potassium level and any type of arrhythmias or arrhythmia grade. Even the eight patients with overt hypokalemia (plasma potassium level 2.5 to 2.9 mmol/L [2.5 to 2.9 mEq/L]) had no worsening of their arrhythmias with diuretic therapy. Arrhythmias worsened in some patients following diuretic therapy but improved in many others. In some patients, there was considerable variability between Holter recordings obtained during the same phase. As shown in Table 6, the number of PVCs per hour varied up to fourfold between consecutive recordings whereas couplets or ventricular tachycardia runs could be present on one but not the other recording. (Individual results for each of the 44 patients are available on request.)

COMMENT

In a previously published study,[6] we found no change in ventricular arrhythmias when overt diuretic-induced hypokalemia was corrected in patients with systemic hypertension. In that study, approximately one third of the patients with overt hypokalemia (average plasma potassium level, 2.8±0.3 mmol/L [2.8±0.3 mEq/L]) had more than minimal ventricular ectopy that remained unaffected by correction of plasma potassium levels. We hypothesized then that those arrhythmias were not related to the low plasma potassium level.

The present study was designed to determine whether diuretic therapy, per se, without hypokalemia or diuretic therapy with hypokalemia has adverse effects on the cardiac rhythm. For the purpose of the study, patients with systemic hypertension and no other major disease were selected. Although ambulatory ECG monitoring represents the best method for detection of spontaneous cardiac arrhythmias, the technique is still limited by considerable day-to-day variability.[16,17] Therefore, to increase its sensitivity, two consecutive 24-hour monitorings were performed during each phase of the study. The close temporal relationship between the plasma potassium measurement and recording of arrhythmias was assured by obtaining blood samples for plasma potassium levels at the beginning and at the end of each 48-hour ECG monitoring. Furthermore, interference with arrhythmias by any other pharmacologic agents was excluded by discontinuing treatment with all medications prior to including patients in the study so that only hydrochlorothiazide was administered during the experimental phase.

Data in this study were examined for the group as a whole and in subgroups; that is, patients were separated into hypokalemic and nonhypokalemic groups and into patients with or without left ventricular hypertrophy. Although we realize the limitations of subgroup analysis, these separations were helpful in differentiating the effects of hypokalemia from any other independent effects of diuretic therapy on the cardiac rhythm and any adverse effects of diuretics in patients with left ventricular hypertrophy.

Results in this study provide no evidence that diuretic therapy or diuretic-induced hypokalemia results in increased ventricular ectopy. Neither the group as a whole nor the subgroups exhibited increased arrhythmias with hydrochlorothiazide therapy. In fact, the hypokalemic group manifested a trend toward decreased arrhythmias with hydrochlorothiazide. More patients had complex arrhythmias at baseline than during hypokalemia. Even the eight patients who exhibited plasma potassium levels of 2.5 to 2.9 mmol/L (2.5 to 2.9 mEq/L) with hydrochlorothiazide therapy did not have any change in the frequency of ventricular ectopy. Two patients with considerable ventricular ectopy at baseline, if anything, improved with diuretic therapy, which also resulted in marked hypokalemia. Patients with left ventricular hypertrophy had considerably more ventricular ectopy at baseline than patients without left ventricular hypertrophy. Although the differences did not reach statistical significance for any individual category of arrhythmias, the average grade per hour was significantly higher in the first group of patients. These findings are in accord with the data published by Messerli et al,[18] who found more severe and complex arrhythmias in hypertensive patients with left ventricular hypertrophy. It is important to emphasize, however, that even patients with left ventricular hypertrophy did not demonstrate increased ventricular ectopy following thiazide therapy.

Data in Table 2 indicate an impressive difference in premature beats at baseline between hypokalemic and normokalemic patients. This difference was not statistically significant due to the large SD. Careful examination of the individual data demonstrated no correlation between baseline arrhythmias and subsequent development of hypokalemia. In fact, the difference at baseline was due to the high premature beat count demonstrated by three patients (257, 76, and 40 PVCs per hour). In the remaining 24 patients constituting the hypokalemic group, baseline PVCs averaged 3.3/h.

Considerable day-to-day variability has been noted in consecutive Holter recordings.[16,17] The sensitivity of the technique increases with the number of monitorings performed. Although a large number of recordings in each phase would be desirable, this is difficult for technical reasons. Most of the previously published studies utilized only one Holter monitoring in each phase, whereas in the present study two recordings were obtained in each phase.

With respect to the variability in arrhythmias noted in this study, the following are noteworthy. The large SD noted in the group as a whole and in the hypokalemic group at baseline has been greatly effected by one patient who demonstrated a very high PVC count at baseline (257/h). This admittedly decreases the statistical power of the study to detect changes. However, if this patient was not to be included, the mean (±SD) of the difference would be 1.2±11.6 for the 43 patients. This would give an 80% statistical power to detect a change of 4.9 premature beats per hour. Although small changes would not have been detected, the clinical significance of such changes is questionable. Furthermore, a trend toward less rather than more arrhythmias was noted after diuretic therapy.

Results in this trial are supported by other similarly designed studies. Lief et al[9] performed 48-hour ECG monitoring in 13 patients with uncomplicated systemic hypertension before and after treatment with hydrochlorothiazide. Plasma potassium levels decreased from 4.0±0.1 to 3.0±0.1 mmol/L (4.0±0.1 to 3.0±0.1 mEq/L), but no change in ventricular ectopy was noted. Madias et al[10] performed 24-hour ECG monitoring in 20 patients with hypertension who were receiving placebo, and at two and four weeks of hydrochlorothiazide therapy. Plasma potassium level was 4.4±0.1 mmol/L (4.4±0.1 mEq/L) with placebo, 3.4±0.1 mmol/L (3.4±0.1 mEq/L) at two weeks, and 3.0±0.1 mmol/L (3.0±0.1 mEq/L) at four weeks of hydrochlorothiazide therapy. Ventricular ectopic activity did not change significantly with hydrochlorothiazide therapy. Caralis et al[19] studied 16 hypertensive patients before and after thiazide therapy. Eight patients with no clinical evidence of organic heart disease had no change in ventricular ectopy following diuretic therapy. The remaining eight patients had findings consistent with organic heart disease and they demonstrated increased ventricular ectopy with diuretics. In a 1983 publication, the Medical Research Council of Britain[20] reported on two studies with rather contradictory results. In the first study, patients with uncomplicated hypertension were subjected to 24-hour ECG monitoring before and after eight to ten weeks of therapy with bendroflumethiazide. This study showed no evidence of increased ventricular ectopy with diuretic treatment. The second study compared results of 24-hour ECG monitoring of patients receiving long-term treatment with thiazides with a group of placebo-treated patients. The investigators noted an overall increased incidence of ventricular ectopy in the diuretic-treated patients. However, this increase in ventricular ectopy could not be attributed to hypokalemia since there was no correlation

with plasma potassium in this particular subgroup and these patients had no baseline pretreatment ECG recordings.

The study most frequently quoted as providing evidence linking diuretic-induced hypokalemia to cardiac arrhythmias is that by Holland et al.[8] That investigation, using 24-hour ECG monitoring, showed increased ventricular ectopy in thiazide-treated, hypokalemic patients, as compared with their control pretreatment recordings. Holland's study, however, failed to take into account the considerable day-to-day variability in arrhythmic activity.[16] Patients with more than six premature ventricular beats per hour at baseline, prior to diuretic therapy, were excluded from the study. Bias, therefore, was introduced by selecting baseline recording with low levels of ventricular ectopy. Because of possible day-to-day variability,[16] the likelihood of finding increased arrhythmias on the second recording would be increased simply due to regression toward the mean rather than to hypokalemia per se. In our study, patients with more than minimal baseline ventricular ectopy were not excluded. It is noteworthy that up to a fourfold difference in the frequency of PVCs was noted in the same patient during the same phase on consecutive 24-hour recordings. More importantly, couplets or runs of ventricular tachycardia were noted on one but not the other 24-hour monitoring during the same phase.

Much of the controversy surrounding diuretic therapy with or without hypokalemia and increased risk of sudden death has been derived from the results of the Multiple Risk Factor Intervention Trial[11] that was published in 1982. That study has been interpreted as having shown increased mortality in a subgroup of patients with ECG abnormalities at rest when aggressively treated with diuretics. Although the authors[11] of that study cautioned that their findings were inconclusive and further investigation was needed, these data have frequently been used as establishing an association between thiazide therapy and increased risk of sudden death in patients with baseline ECG abnormalities.[21] This finding, however, has not been substantiated by other studies. In fact, the recent retrospective analysis of the Hypertension Detection and Follow-up Program[22] failed to confirm the findings of the Multiple Risk Factor Intervention Trial. Furthermore, the final report of the Medical Research Council[23] reporting on the results of treatment of mild hypertension could not demonstrate any adverse effects of diuretic therapy on patient mortality.

Although the electrophysiologic changes associated with diuretic therapy are of uncertain significance, theoretically at least, it is possible that mild-to-moderate, diuretic-induced hypokalemia in patients with uncomplicated systemic hypertension could be associated with more electrical stability and less cardiac arrhythmias. It has been shown by many investigators that diuretic therapy is mainly associated with a decrease of extracellular potassium but only minimal change in intracellular potassium concentration.[24-27] The changes result in hyperpolarization of the cell membrane,[28,29] which could lead to an increased threshold of excitation, increased rate of rise of phase 0, and improvement in conduction, which could eliminate reentrant circuits and thus improve electrical stability.

In conclusion, the results of this study provide no evidence that diuretic therapy, per se, or mild-to-moderate, diuretic-induced hypokalemia are associated with increased ventricular ectopy. Furthermore, diuretic therapy did not result in increased ventricular ectopy in patients with left ventricular hypertrophy, although these patients appear to have more arrhythmias at baseline as compared with patients with normal left ventricular wall thickness.

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